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A Derivative UV Spectrophotometry Approach for the Estimation of Tapentadol Hydrochloride and Paracetamol in Marketed Formulation

Bhupendra Singh*, Bharat Jhanwar, Geetanjali Saini

Lovely Faculty of Applied Medical Sciences, Lovely University, Jalandhar (Punjab)-140001, India

Abstract : A simple, rapid, precise and accurate derivative spectrophotometric method has been developed for simultaneous analysis of Paracetamol (PCM) and Tapentadol (TAP) in their combined dosage form. First order derivative method involves measurement of absorbance at 257.60 nm (for TAP) and 289.20 nm (for PCM) in first order derivative spectra. Developed method was validated according to ICH guidelines. The calibration graph follows Beer's law in the range of 1.0 to 13.0 µg/ml for Tapentadol and 6.5 to 39 µg/ml for Paracetamol with R square value greater than 0.998. The accuracy of themethod was determined by recovery studies and showed % recovery between98 to 102%. Intraday and inter day precision was checked for the method and mean %RSD was found to be less than 2 for this methods. The method was successfully applied for estimation of Paracetamol and Tapentadol in the marketed formulation.
Key words: Tapentadol hydrochloride, Paracetamol, First order derivative, D-value.

Introduction

Tapentadol (TAP) chemically is 3 - [(1R, 2R) -3 - (dimethylamino) –1 - ethyl-2 -methylpropyl] phenol hydrochloride (**Fig. 1**), is an agonist at the µ-opioid receptor and as a norepinephrine reuptake inhibitor. This dual mode of action provides analgesia at similar levels of more potent narcotic analgesics such as hydrocodone, oxycodone, and morphine, but with more tolerable side effect profile[1-4]. Paracetamol (PCM) chemically is N-(4-hydroxyphenyl) ethanamide (**Fig. 2**), used as antipyretic and analgesic [5]. Paracetamol is official in British Pharmacopoeia 2012, Europan Pharmacopoeia-2011, Indian Pharmacopoeia-2010, and United State Pharmacopoeia. [6-10]Officialmethods for assay are UV- spectrophotometric and by liquid chromatography reported in British Pharmacopoeia. Official method of Tapentadol hydrochloride was reported in Indian Pharmacopoeia. Different methods like UV-Spectrophotometry, HPLC have been reported for the estimation of both the drugs as asingle component as well as in combination with other drugs like Aceclofenac,Ondansetron Lornoxicam, Nimesulide, Metoclopramide hydrochloride, Tramadol, [11-17].

However no official method was reported for estimation of TAP and PCM in marketed formulations by derivative U.V spectroscopy. In the present work, it is proposed to develop a simple validation of first derivative UV-Spectrophotometry method for simultaneous estimation of Tapentadol hydrochloride and Paracetamol as API and in combination in tablet dosage form.

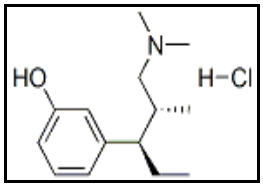

Fig. 1 Tapentadol Hydrochloride

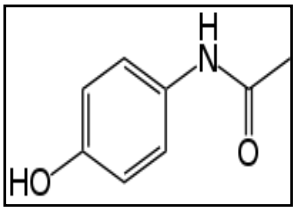

Fig. 2 Paracetamol

Materials and Methods:

Equipment and materials: Shimadzu UV-1800 double beam spectrophotometer with computer display having UV Probe 2.31 software and a matching pair of quartz cuvette (Shimadzu Corporation, Kyoto, Japan). All weights were measured on digital balance GR-100 (A&D Comp. Ltd.) with a minimum weighing capacity of 1mg was used in the study. Sodium Hydroxide obtained from Merck Limited, Maharashtra, India and distilled water was obtained in-house laboratory.

Methods:

Preparation of Stock Solutions:

Accurately weighed TAP (25 mg) was dissolved in 0.1N Sodium hydroxide and transferred to 25 ml volumetric flask to obtain as tock solution of TAP (1000 µg/mL). It is further diluted one part in 100 to produce a final solution containing 10 µg per ml of TAP. Paracetamol (10 mg) was dissolved in same solvent and transferred to 100 ml volumetric flask to obtain a stock solution of PCM (100 µg/ml).

First Order Derivative Method:

The solutions of standard PCM and TAP were prepared in the range of 1 to 13µg/ml & 6.5 to 39µg/ml respectively. The absorption spectra of the solutions of PCM and TAP were recorded in the range of 200 nm to 400 nm and the instrument was transformed to first derivative with $\Delta\lambda$ = 2nm and scaling factor 200 (Fig. 3, 4, 5).The zero crossing point of TAP and PCM were determined to be at 289.2nm and 257.6nm respectively. The amplitudes at 257.60 nm were plotted against respective concentrations of TAP and the amplitudes at 289.20 nm were plotted against the respective concentrations of PCM for the preparation of calibration graph. Calibration graph for TAP and PCM are shown (Fig. 6 & 7).

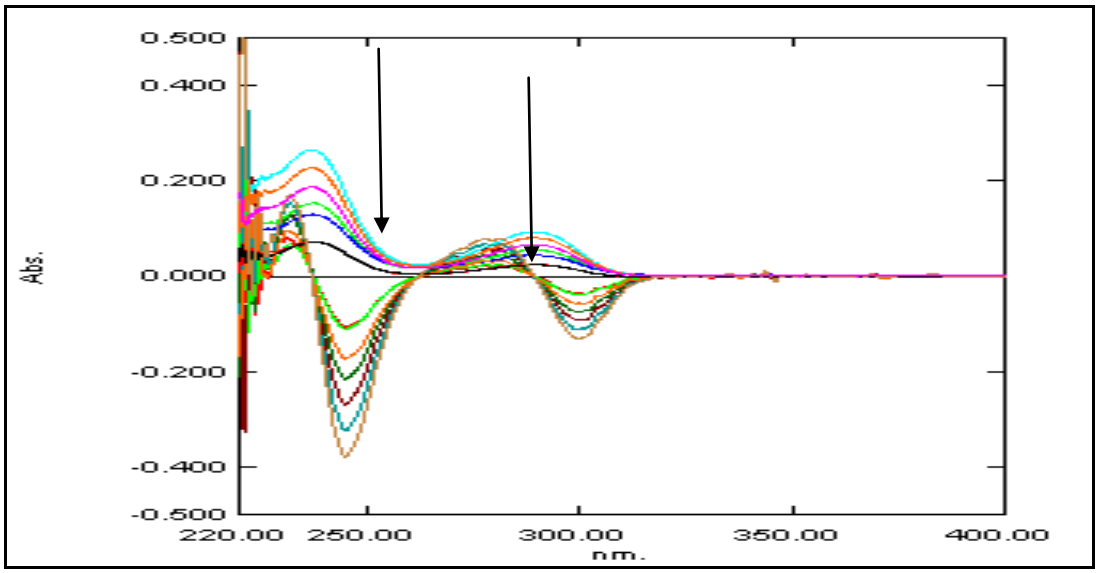

Fig. 3: Wavelength scans for determination of zero crossing point of Tapentadol

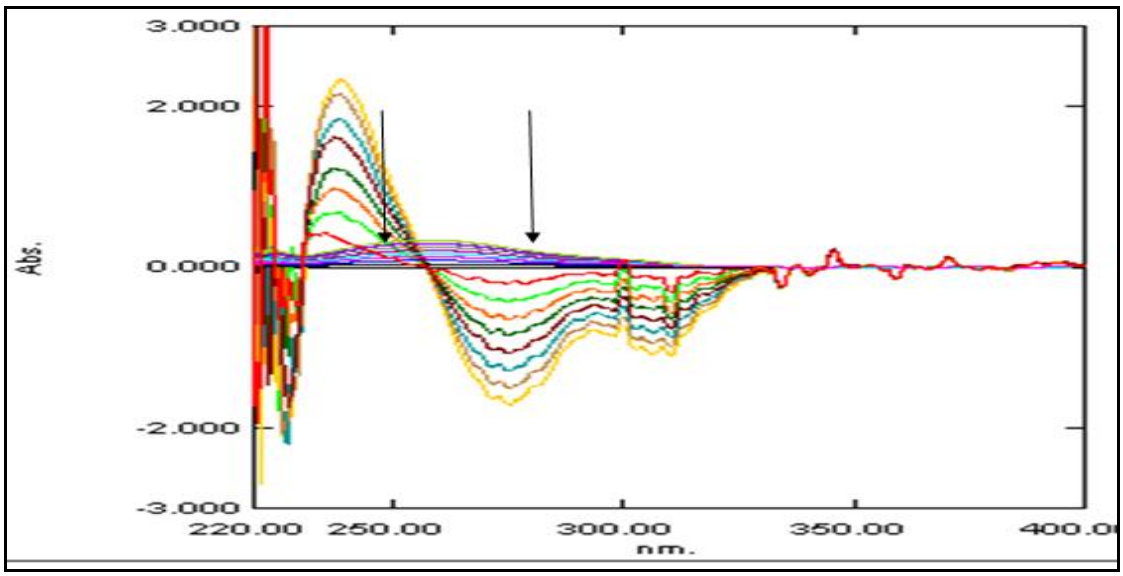

Fig 4: Wavelength scan for determination of zero crossing point of Paracetamol

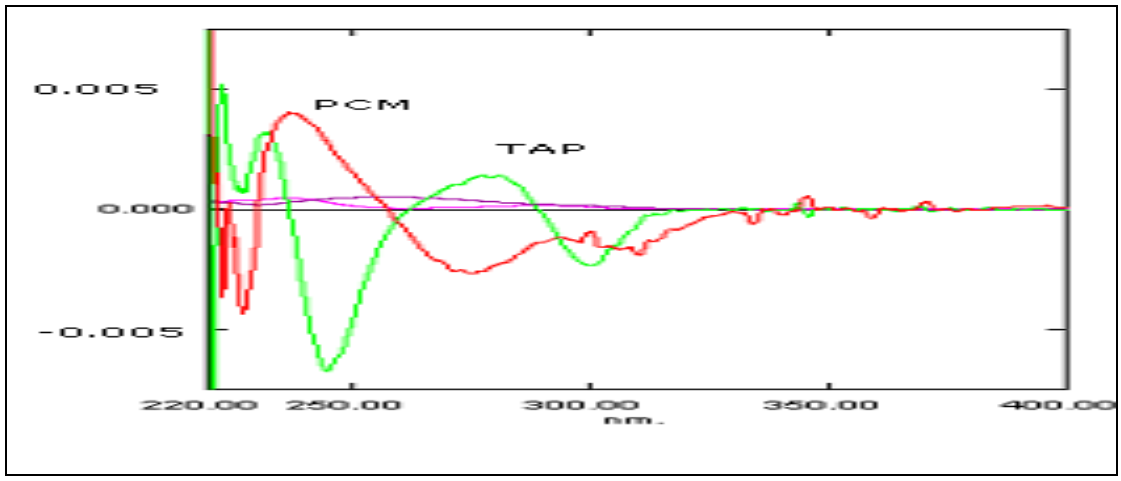

Fig. 5: First order derivative spectra of TAP and PCM

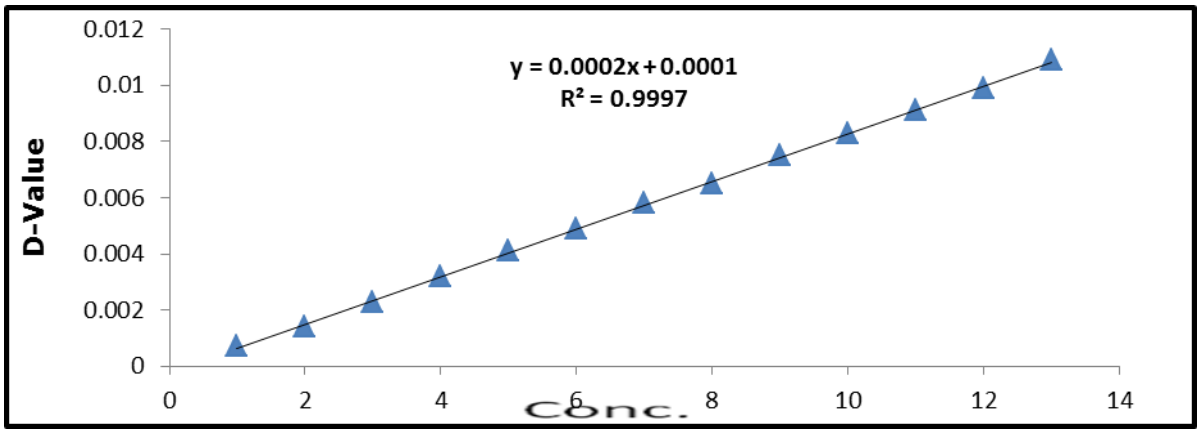

Fig.:6 Standard curve of Tapentadol hydrochloride (257.6nm)

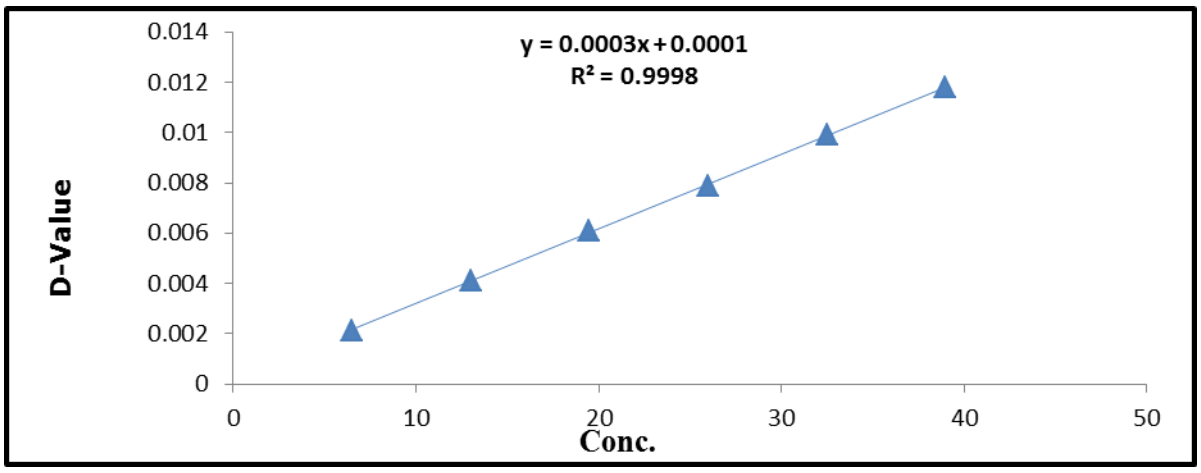

Fig.7:Standard curve for Paracetamol (289.20 nm)

ICH Validation Characteristics:

The developed method has been validated in terms of linearity, range, specificity, accuracy, precision, assay, LOD and LOQ as per ICH Q2 (R1) guidelines

1. Linearity

Appropriate aliquots of TAP and PCM standard stock solution were transferred to avolumetric flask of 10 ml capacity. The volume was adjusted to the mark with Sodium hydroxide. All absorbance were measured at 257.6 nm and 289.2nm respectively. Calibration curves were constructed by plotting average absorbance (n=6) versus concentrations for both drugs. Straight line equations were obtained from these calibration curves.

2. Range

The range of an analytical method is defined as the interval between upper and lower levels.

Working range**:** It begins from limit of quantitation to the maximum concentration used for the development of the analytical method.

Linearity range**:** It is the interval in which the response is directly proportional to the concentration between the upper and lower levels.

Target concentration**:** It is defined as the concentration, which is equal to the midpoint of linearity range.

Target range**:**It is that concentration which is 80%, 100% and 120% of the target concentration.

The various ranges have been reported below.

3. Specificity

Commonly used excipients (lactose, starch, magnesium stearate and talc) were added into a pre-weighed quantity of standard drug mixture (1:6.5) and then D-values were measured before and after addition of excipients. Calculations were done to determine the quantity of the drugs and the interferences of additives on D-values.

4.Accuracy

Accuracy was determined from therecovery of the method by spiking of standard drug mixture of TAP and PCM (1:6.5). Each concentration was analysed 6 times and average recoveries are calculated.

5. Precision

Repeatability: It indicates the precision under the same operating conditions over a short interval of time and inter-assay precision. Repeatability was performed for six times with single concentration ratio (4:22.75) in the mixture.

Intermediate Precision: It includes intra-day studies which mean determination of the concentration of drug mixture on the same day with an interval of three hours whereas inter-day means the calculation of drug contents on three different days in the ratio of 4:22.75.

6. The sensitivity of method: Detection and quantitation limits define the sensitivity of developed method. It has been determined from the linearity data and standard deviation as per ICH guidelines.

7. Assay:

20 tablets of "Vorth-TP Plus" (Glenmark Pharmaceuticals) were weighed correctly and crushed to fine powder using a glass mortar and pestle. A portion equivalent to about 25 mg of Tapentadol & 162.5 mg of PCM were correctly weighed and transferred to 500 ml volumetric flask. Proper dilutions were done up to 3.5µg/ml and 22.75 µg/ml of TAP and PCM respectively and absorbance were measured (n=6). Percent weight claim of tablet was determined by using equation 1 and 2. The results are given in table 8.

Results and Discussions

Linearity and range

Linearity range was found to be 1-13µg/ml for Tapentadol hydrochloride and 6.5-39µg/ml for Paracetamol at 257.60nm & 289.20nm. The correlation coefficient was found to be 0.9997 & 0.9998 for TAP and PCM at 257.60nm & 289.20nm respectively, which reveals a good linearity range. The slope was found to be 0.0002 & 0.00003 for TAP and PCM and intercept 0.0001 & 0.0001 for TAP and PCM, which were close to zero intercepts (Table 1.).

Table 1: Estimation of Tapentadol Hydrochloride & Paracetamol in marketed formulation

S.N	Label Claim (Vorth TP)	D-Value		Conc. Made (µg/ml)		Amt. found In mg		% Recovery		% mean recovery ± SD	
		A_1 257.6	A_2 289.2	TAP 3.5 (µg/ml)	PCM 22.75 (µg/ml)	TAP	PCM	TAP	PCM	TAP	PCM
	TAP (50) + PCM (325)	0.0029	0.0070	3.50	22.75	3.51	22.74	99.95	100.28	3.50 ± 0.303	22.76 ± 0.419
		0.0028	0.0069	3.51	22.81	3.51	22.81	100.0	100.0		
		0.0030	0.0072	3.49	22.68	3.51	22.81	100.25	100.5		
		0.0028	0.0068	3.52	22.88	3.50	22.75	99.43	99.43		
		0.0031	0.0070	3.49	22.68	3.50	22.74	100.26	100.28		
		0.0026	0.0076	3.50	22.75	3.49	22.74	99.95	99.71		

** TAP: - Tapentadol hydrochloride, PCM: - Paracetamol,* **n=6 ± SD**

Table 2: Data for specificity

S. No.	TAP : PCM	% Interference	
		TAP (257.60 nm)	PCM (289.20 nm)
1	1:6.5	0.282	0.288
2	2:13	0.347	0.270
3	3:19.5	0.358	0.182
4	4:26	0.273	0.124
5	5:32.5	0.237	0.118
6	6:39	0.232	0.132
Mean		**0.242**	**0.175**

Specificity:

The developed method was specific as percent mean interference was found to be 0.242 and 0.175 for TAP and PCM respectively, which is less than 0.5 % as per ICH guidelines (Table 2.).

Precision:

Repeatability study showed a % R.S.D of 1.7241 for TAP and 1.449 % for PCM, which is less than 2%. Thus, it can be concluded that the analytical technique showed a good repeatability precision study. The intra-day precision study showed a mean % R.S.D of 0.282 for TAP and 0.046 for PCM, which is less than 2%. Thus, it can be concluded that the analytical technique also showed a good intra-day precision study. Inter-day precision study showed a mean % R.S.D of 0.282 for TAP and 0.129 % for PCM, which is less than 2%. Thus, it can be concluded that the analytical technique showed a good inter-day precision study.(Table.4)

Table 3: Accuracy Study

A.P.I. TAP:PCM 1 : 6.5	Spiking concentration (ppm) 1:6.5	Mean % Recovery	% R.S.D.
TAP	1, 2 & 3	99.74 ± 0.4172	0.417
PCM	6.5, 13 & 19.5	98.75 ± 3.4340	0.434

n=6 ± SD

Table 4: Precision Study

Parameters	Tapentadol hydrochloride	Paracetamol
	257.60 nm	**289.20 nm**
Repeatability	1.7241%	1.449%
Intra-day	0.282	0.046
Inter-day	0.282	0.129

Accuracy:

The accuracy study (recovery method) indicated that the mean of the % recovery was 99.74 and 98.75 and % R.S.D was 0.417 and 0.434 for Tapentadol hydrochloride and Paracetamol respectively in the mixture.

Sensitivity:

The Limit of detection(LOD) was found to be 0.799µg/ml and 0.792µg/ml and limit of quantitation (LOQ) was found to be 2.424µg/ml and 2.400µg/ml for TAP and PCM respectively which represents that sensitivity of the method is high.

Assay:

Table 5: Validation parameters as per ICH-Q2 (R1) guidelines for Tapentadol Hydrochloride & Paracetamol.

Parameters	Tapentadol Hydrochloride	Paracetamol
	257.60 nm	**289.20**
Specificity	0.242	0.175
Range		
Beers law limit	1-13	6.5-39
Linear range	1-13 µg/ml	6.5-39 µg/ml
Slope	0.0002	0.0003
Intercept	0.0001	0.0001
Correlation coefficient	0.9997	0.9998

Working Range	2.424 to 13 µg/ml	2.400 to 39 µg/ml
Target Concentration	7 µg/ml	22.75 µg/ml
Target Range	5.6 µg/ml, 7 µg/ml, 8.4 µg/ml	18.2 µg/ml, 22.75 µg/ml, 27.3 µg/ml
Precision (%RSD)		
Repeatability	1.7241%	1.449%
Intra Day	0.282	0.046
Inter Day	0.282	0.129
Accuracy	99.74 ± 0.417	98.75 ± 0.429
LOD	0.799 µg/ml	0.792 µg/ml
LOQ	2.424 µg/ml	2.401 µg/ml
Assay	99.97	100.04

Conclusion:

A simple and economic U.V. spectrophotometric method has been successfully developed for the estimation and was found to be specific, accurate and precise as well as having good reproducibility. It has followed all the parameters for validation as per ICH (Q2R1) guidelines. Hence, the developed method can be used as aroutine analysis of any marketed tablet dosage form of the given combination.

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